Individualization of Piperacillin Dosage in a Tertiary Care Centre: Benefits of Therapeutic Drug Monitoring With or Without Model-Informed Precision Dosing

Haefliger D.[1], Mina L.[1,2], Guidi M.[1,2], Csajka C.[2,3], André P.[1], Rothuizen L.E.[1], Marzolini C.[1,4,5], Decosterd L.A.[1], Thoma Y.[6], Girardin F.[1], Buclin T.[1]

[1] Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.
[2] Centre for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.
[3] School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland
[4] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland.
[5] Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom.
[6] School of Engineering and Management Vaud, University of Applied Sciences and Arts Western Switzerland (HES-SO), Yverdon-les-Bains, Switzerland.

Background
Model-Informed Precision Dosing (MIPD) software, such as TUCUXI, combine prior knowledge from population PK (popPK) models with individual data from therapeutic drug monitoring (TDM) to issue optimal dosage adjustment. At our tertiary care centre, piperacillin TDM was performed empirically so far. The piperacillin popPK model by Chen (2016) has now been implemented into TUCUXI. This study aimed to evaluate the performance of TDM and MIPD for piperacillin trough concentration target attainment.

Methods
This single-centre retrospective observational study involved adult patients with intermittent short intravenous infusions of piperacillin and two available TDM measurements. We retrospectively applied MIPD using TUCUXI to all patients and obtained six dosage strategies: same dosage for all patients (piperacillin 4 g TID), actual initial dosage (based on a reference dosing chart), actual empirical dosage adjustment following 1st TDM, *a priori* MIPD-based dosage, *a posteriori* MIPD-based adjustment after 1st TDM, and MIPD-based recommendation based on both TDM values. The six dosing strategies were compared regarding piperacillin daily dose, trough concentrations distribution and probability of target attainment (PTA) defined as maintenance of trough concentration between 8 and 32 mg/L. This concentration range served as a surrogate to maintain free piperacillin levels above the minimum inhibitory concentration for most bacteria throughout entire dosing interval.

Results
The analysis included 78 courses of piperacillin with 2 TDM measurements. Median piperacillin trough concentrations fell within target range (8-32 mg/L) for all strategies except *a priori* MIPD-based dosage (median 42.2 mg/L, IQR 28.5–77.6 mg/L). Distributions of trough concentrations showed significant differences between the six dosing strategies: in particular, MIPD-based dosing strategies best reduced standard deviation (SD) of trough concentrations ($p < 0.001$). SD of daily doses correlated inversely with SD of trough concentrations. PTA of 32%, 32%, 55%, 29%, 83%, and 94% were estimated respectively for the six dosing strategies mentioned above ($p < 0.001$).

Conclusions
Our observations and simulations show better PTA and standardization of exposure with empirical TDM versus no TDM, and further improvement with MIPD. Further large-scale prospective studies are needed to validate MIPD benefits for both target attainment and clinical outcomes.

Key Words: TDM**,** MIPD, target attainment, piperacillin

Count: 350 words